Regio- and Stereo-specificity of Nucleophilic Attack on Steroidal π-Allylpalladium Complexes

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Reaction of α- and β-1—3-η-type steroidal π-allylpalladium complexes with AcOK yielded products resulting from *trans*-attack on the side opposite to the co-ordinated palladium, while reaction of steroidal olefins with $PdCl_2$-$CuCl_2$-AcOK/AcOH afforded products arising from *cis*-attack.

MUCH work has been reported on stereospecific nucleophilic substitution in π-allyl-and π-olefin-palladium complexes.[1-11] It was therefore of interest to ascertain whether the nucleophilic attack on such compounds is *cis* or *trans*. To this end we have investigated the stereospecificity of nucleophilic substitutions in steroidal π-allylpalladium complexes. Earlier, we reported [12,13] that cholestene derivatives with palladium(II) chloride in the presence of potassium acetate in acetic acid afforded the corresponding steroidal palladium complexes, and oxidation of these complexes using chromium(VI) oxide in *NN*-dimethylformamide (DMF) readily gave the corresponding α,β-unsaturated ketone in good yield.

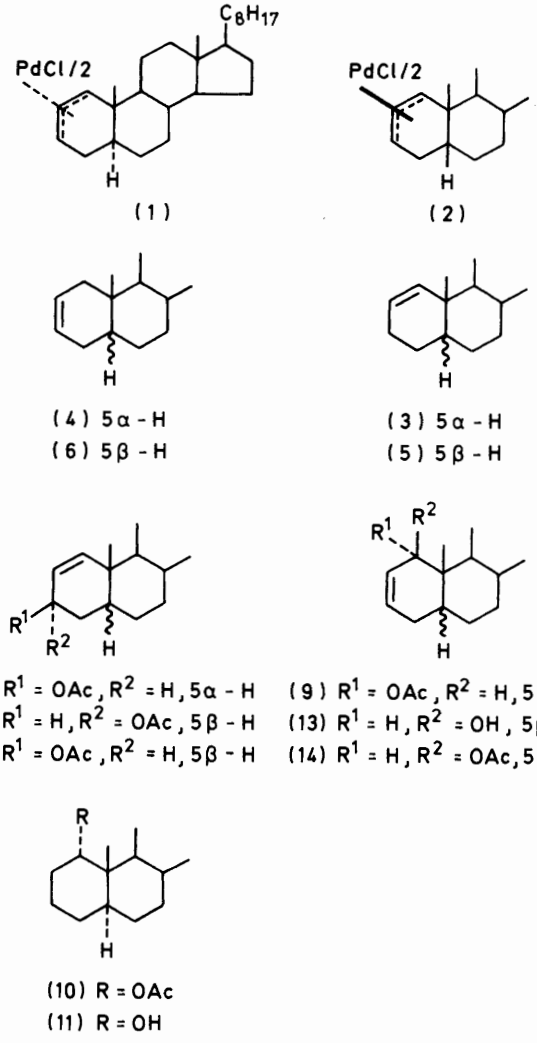
More recently, Bäckvall *et al.*[11] reported that the reaction of the π-allyl (methoxycyclohexenyl)palladium complex with AcOAg gave the allylic acetate in which the π-allyl ligand had been attacked from the same side as the metal (*cis*-addition). Moreover, they described the stereocontrolled *trans*- and *cis*-addition by acetoxy-ion to π-allyl complexes.[14]

Here, we describe the reactions of the complexes di-μ-chloro-bis[(1—3-η-5α-cholesten-2α-yl)palladium(II)] (1) and di-μ-chloro-bis[(1—3-η-5β-cholesten-2β-yl)palladium(II)] (2) with AcOK/DMF and also the reactions of 5α-cholest-1-ene (3), -2-ene (4), 5β-cholest-1-ene (5), and -2-ene (6) with $PdCl_2$-$CuCl_2$-AcOK/AcOH.

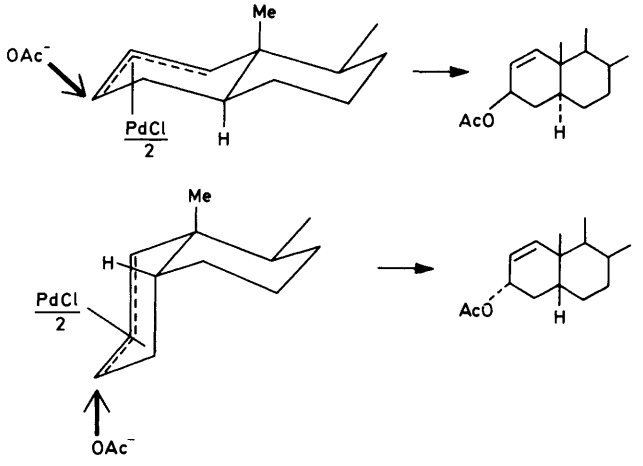
The reaction of the α-1—3-η-type complex (1) with AcOK in DMF at 40—45 °C for 8 h yielded 3β-acetoxy-5α-cholest-1-ene (7), m.p. 84—85 °C (lit.,[15] m.p. 84—87 °C). In the case of the β-1—3-η-type complex (2), the allyl acetate (8), m.p. 113—114 °C was obtained. This product was presumed to be 3α-acetoxy-5β-cholest-1-ene, identification being based on the presence of a multiplet in the n.m.r. spectrum at δ 5.25—5.60 (3-H).

These results show that the nucleophilic substitution of the α- and β-1—3-η-type complex with AcOK which yields the product due to *trans*-attack on the side opposite to the co-ordinated palladium; this occurs in the direction of C-3, for reasons of greater flexibility and reduced steric hindrance (see Scheme 1).

On the other hand, to investigate nucleophilic substitution in the steroidal π-olefin palladium complex, the reaction of steroidal olefins with $PdCl_2$-$CuCl_2$-AcOK/AcOH was carried out. 5α-Cholest-1- (3) and -2-ene (4) were each treated with $PdCl_2$, $CuCl_2$, and AcOK in AcOH under refluxing for 33 h. Both reactions yielded the same acetoxycholestene derivative (9), which was then converted into 1α-acetoxy-5α-cholestane (10) by reduction with H_2/Pd-C. Hydrolysis of compound (10) gave 1α-hydroxy-5α-cholestane (11), m.p. 104—105 °C (lit.,[15] m.p. 102—106 °C). In the case of both 5β-cholest-1-ene (5) and -2-ene (6), 3α-acetoxy-5β-cholest-1-ene (8) and compound (12), m.p. 71—73 °C, were given in *ca.* 1 : 1 ratio. Compound (12) was presumed to be the 3β-acetoxy-1-ene derivative, on the basis of a signal in the ^{1}H n.m.r. spectrum at δ 5.21 (multiplet, *W*/2 9 Hz, 3α-H).



These results show that in the reactions of 5α-cholest-1-ene and -2-ene, and 5β-cholest-1-ene and -2-ene with $PdCl_2$-$CuCl_2$-AcOK/AcOH, *cis*-attack occurs in the direction of C-1. It is known that 5α- and 5β-cholest-1-ene are isomerized to the more stable 2-ene compound.[12]



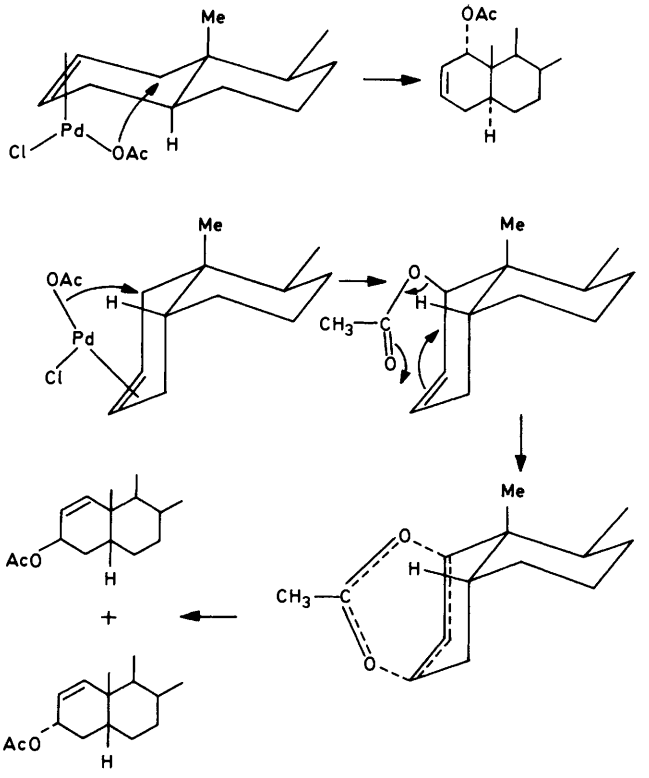
SCHEME 1

It is considered that in the reactions of 5α- and 5β-cholest-2-ene with this reagent, the 5α-product was an α-π-palladium complex intermediate, in which the palladium was co-ordinated at the α-face, while the 5β-product was a β-π-palladium complex intermediate, in which the palladium was co-ordinated at the β-face. Both complexes then underwent displacement of a C-1 axial substituent rather than of one in the C-4 position, caused by a nucleophilic attack of acetoxy-ion from the *cis*-side. It was assumed that 1β-acetoxy-5β-cholest-2-ene (14) produced as an intermediate would rearrange easily to the 3β-compound. In order to clarify this mechanism, 1β-acetoxy-5β-cholest-2-ene (14) was synthesized by the acetylation of 1β-hydroxy-5β-cholest-2-ene (13)[17] with acetic anhydride–pyridine. The rearrangement of the acetoxy-compound (14) under conditions of allylic acetoxylation as described for compounds (5) or (6) above yielded 3α- (8) and 3β-acetoxy-5β-cholest-1-ene (12) in a ratio of *ca.* 1 : 1 (Scheme 2). Such rearrangement is similar to the properties of 1β-halogeno-5β-cholestan-2-one[16] and 1β-hydroxy-5β-cholest-2-ene,[17] which give the 3-substituted rearrangement products.

Thus, on the basis of all of the foregoing results, it was concluded that the reaction of α- and β-1—3-η-type steroidal π-allylpalladium complexes with AcOK yields products due to *trans*-attack on the side opposite to the co-ordinated palladium, and occurs in the direction of C-3. It was further concluded that the reaction of 5α-cholest-1-ene and -2-ene, and 5β-cholest-1-ene and -2-ene with $PdCl_2$-$CuCl_2$-AcOK/AcOH affords products due to *cis*-attack, which occurs at the C-1 axial position.

EXPERIMENTAL

All the melting points are uncorrected. The i.r. spectra were measured using a Hitachi Model 215 grating infrared



SCHEME 2

spectrometer. The n.m.r. spectra were measured using either Hitachi–Perkin Elmer R-20A or Hitachi Model R-900 (FT-n.m.r.) spectrometers in carbon tetrachloride and deuteriochloroform, with TMS as the internal standard. The high-resolution mass spectra were recorded at 75 eV on a JEOL JMS–O1SG-2 instrument with a direct inlet.

Materials.—The steroidal π-allylpalladium complexes were synthesized by the methods described in the previous paper.[13]

The following compounds were synthesized by the methods described in the literature: 5α-cholest-1- (3),[18] -2-ene (4),[18] 5β-cholest-1-ene (5),[19] and -2-ene (6).[19]

Reaction of Di-μ-chloro-bis[(1–3-η-5α-*cholesten*-2α-*yl*)*palladium*(II)] (1) *and Potassium Acetate in* NN-*Dimethylformamide.*—The π-allylpalladium complex (1) (470 mg) in *NN*-dimethylformamide (47 ml) was treated with potassium acetate (2.1 g) at 40–45 °C for 8 h. After the usual work-up, the resulting oil was chromatographed on silica gel (10 g). Elution with hexane (100 ml) and benzene (80 ml) gave the 3β-acetoxycholestene (7) as plates (142 mg), m.p. 84—85 °C (lit.,[15] 84—87 °C). The i.r. and n.m.r. spectra were identical with those of an authentic sample.

Reaction of Di-μ-chloro-bis[(1—3-η-5β-*cholesten*-2β-*yl*)*palladium*(II)] (2) *and Potassium Acetate in* NN-*Dimethylformamide.*—The reaction of the complex (2) (210 mg) and potassium acetate was carried out for 32 h using the technique described above. The resulting oil was purified by preparative t.l.c. on silica gel plates (2 mm layer) (E. Merck). Elution with benzene gave the 3α-acetoxycholestene (8) as needles (64 mg) from ethanol, m.p. 113—114 °C; $\nu_{max.}$ (KBr) 1 736 and 1 244 cm^{-1}; δ ($CDCl_3$) 2.06 (3 H, s), 5.45 (1 H, d, *J* 9 Hz), 5.25—5.60 (1H, m, *W*/2 18 Hz), and 5.76 (1 H, d,

J 9 Hz) (Found: C, 81.9; H, 11.2%; M^+, 428.365 8. $C_{29}H_{48}O_2$ requires C, 81.3; H, 11.3%; *M*, 428.365 2).

Reaction of 5α-*Cholest*-1- (3) *or* -2-*ene* (4) *with Palladium*(II) *Chloride, Copper*(II) *Chloride, and Potassium Acetate in Acetic Acid.*—A mixture of compounds (3) or (4) (1.00 g), palladium(II) chloride (192 mg), copper(II) chloride (2.30 g), and potassium acetate (2.65 g) in acetic acid (50 ml) was refluxed with stirring for 33 h. The solvent was then removed under reduced pressure and the residue was poured into water and extracted with diethyl ether. The ethereal solution was washed with aqueous sodium hydrogen carbonate and with water, and then dried and evaporated. The resulting oil (1.136 g) was chromatographed on silica gel (50 g). Elution with benzene gave the allyl acetate (9) as a colourless oil (492 mg). Attempts to crystallize the allyl acetate were unsuccessful, and so it was used in the next step without purification; $\nu_{max.}$ (film) 3 026, 1 730, 1 655, and 1 240 cm^{-1}; δ (CCl_4) 1.96 (3 H, s), 4.75 (1 H, m, *W*/2 6 Hz), and 5.77 (2 H, d, *J* 3 Hz).

Confirmation of Configuration of 1α-*Acetoxy*-5α-*cholest*-2-*ene* (9).—The allyl acetate (9) (300 mg) in ethanol (50 ml) was treated with hydrogen using 10% palladium on charcoal (300 mg) as a catalyst. After the usual work-up, attempts to crystallize the resulting oil (10) (295 mg) were unsuccessful, and so it was used for the next step without purification; $\nu_{max.}$ (film) 1 733 and 1 241 cm^{-1}; δ (CCl_4) 4.71 (1 H, m, *W*/2 5 Hz). The acetoxy-compound (10) (290 mg) in ethanol (50 ml) was treated with a solution of potassium hydroxide (100 mg) in the same solvent (5 ml), and the mixture was refluxed for 30 min. The ethanol was removed under reduced pressure and the residue was then diluted with water and extracted with diethyl ether. The ethereal solution was washed with water, dried, and evaporated under reduced pressure. Crystallization of the residue from ethanol gave the 3β-alcohol (11) as plates (167 mg), m.p. 104—105 °C (lit.,[13] 102—106 °C). The i.r. and n.m.r. spectra were identical with those of an authentic sample.

Reaction of 5β-*Cholest*-1- (5) *or* -2-*ene* (6) *with Palladium*(II) *Chloride, Copper*(II) *Chloride, and Potassium Acetate in Acetic Acid.*—A mixture of compounds (5) or (6) (200 mg), palladium(II) chloride (38 mg), copper(II) chloride (460 mg), and potassium acetate (530 mg) in acetic acid (10 ml) was treated according to the procedure described for the allylic acetoxylation of compounds (3) or (4). After the usual work-up, the resulting oil (210 mg) was purified by preparative t.l.c. on silica gel plates (2 mm layer) (E. Merck). Elution with benzene gave the 3α-acetoxycholestene (8) as needles (46 mg) from ethanol, m.p. 113—114 °C, and the 3β-acetoxycholestene (12) as needles (62 mg) from ethanol, m.p. 71—73 °C; $\nu_{max.}$ (KBr) 1 736 and 1 244 cm^{-1}; δ ($CDCl_3$) 2.04 (3 H, s), 5.45 (2 H, m), 5.50—5.80 (1 H, m), and 5.95 (1 H, d, *J* 12 Hz) (Found: C, 80.9; H, 11.9%; M^+, 428.360 5. $C_{29}H_{48}O_2$ requires C, 81.3; H, 11.3%; *M*, 428.365 2).

1β-*Acetoxy*-5β-*cholest*-2-*ene* (14).—1β-Hydroxy-5β-cholest-2-ene (13) [17] (100 mg), prepared according to the procedure reported earlier, was treated with acetic anhydride (10 ml)–pyridine (10 ml) for 10 h at room temperature. After the usual work-up, the resulting oil, on crystallization from ethanol, gave the 1β-acetoxycholestene (14) as needles (56 mg) from ethanol, m.p. 110—112 °C; $\nu_{max.}$ (KBr) 1 724 and 1 250 cm^{-1}, δ ($CDCl_3$) 2.02 (3 H, s), 5.16 (1 H, d, *J* 6 Hz), and 5.75—5.95 (2 H, m) (Found: C, 80.8; H, 12.0%; M^+, 428.366 8. $C_{29}H_{48}O_2$ requires C, 81.3; H, 11.3%; *M*, 428.365 2).

Reaction of 1β-*Acetoxy*-5β-*cholest*-2-*ene* (14) *with Palladium*(II) *Chloride, Copper* (II), *Chloride, and Potassium Acetate in Acetic Acid.*—A mixture of compound (14) (30 mg), palladium(II) chloride (5 mg), copper(II) chloride (60 mg), and potassium acetate (69 mg) in acetic acid (5 ml) was treated according to the procedure described for the acetoxylation of compounds (5) or (6). After the usual work-up, the resulting oil was purified by preparative t.l.c. on silica gel plates (2 mm layer) (E. Merck). Elution with benzene gave the 3α-acetoxycholestene (8) as needles (9 mg) from ethanol, m.p. 113—114 °C and the 3β-acetoxycholestene (12) as needles (7 mg) from ethanol, m.p. 71—73 °C.

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